relevant features of human *H. pylori* infection and pathology. Using this model, we have shown that gastric disease is induced only by infection with type I bacteria. This result is in agreement with serological data showing that most people with duodenal ulcers have antibodies specific for type I bacteria, and it confirms our previous findings with bacterial lysates or purified cytotoxin (9). Finally, we have shown that infection by both type I and type II bacteria can be prevented by oral immunization. This finding suggests that vaccines against *H. pylori* are feasible and provides the rationale to proceed with human clinical trials. The mouse model described here will allow the study of the pathogenesis of *H. pylori* infection and the development of therapeutic agents and vaccines.

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25. Mice were inoculated orally with saline or different fresh isolates of *H. pylori*. Fresh isolates of type I and type II bacteria were cultured from biopsies of patients with chronic gastritis. No correlation could be made between the type of *H. pylori* that was isolated and severity of disease, because patients were often infected by several strains. The biopsies were streaked onto Columbia agar with 5% horse blood, 0.2% cyclodextrin, and Dent's or Skirrow's antibiotic supplement (Oxoid, Basingstoke, UK), and isolation of *H. pylori* strains was performed according to standard procedures (6). Single colonies for each isolate were then grown and expanded. The primary colonization experiments were performed with strains that had never been frozen. Before infection, blood samples were drawn from all mice for serological assessment of their preimmune status. Mice were then given 0.25 ml of a solution of 0.2 M $NaHCO_3$ orally, through a sterile gastric gavage, to neutralize acidity. Through the same route, 10^9 CFUs of each strain in 0.15 ml of sterile saline were administered immediately after the bicarbonate treatment. A control group of mice received the same amount of sterile saline alone. The same treatment was repeated after 3 and 5 days. Mice were purchased from Charles River (Calco, Italy) and were housed in our animal facilities with a 12-hour light-dark schedule. Animals had free access to sterile water and food but were not allowed to eat for 24 hours before each treatment as well as before killing. The coprophagic behavior of mice was not restrained except during the fasting periods. At the time of killing, a blood sample was drawn from each mouse to assess their postinfection immune status. Animal treatments and care were given in accordance with institutional guidelines. Infection in a given mouse was assessed as follows: The stomach was removed and opened through the lesser curvature using sterile surgical instruments; the forestomach, containing nonmucosal epithelial squamous tissue, was eliminated. The whole mucous surface of the remaining gastric tissue was gently streaked onto an agar plate that was then incubated for 3 to 5 days at 37°C under microaerophilic conditions (Oxoid). Growing bacteria were identified as *H. pylori* on the basis of Gram staining and the production of urease and catalase. Some contaminant Gram-negative microaerophilic bacteria were present in the cultured plates, but they could be easily discriminated from *H. pylori* through inspection of the colony morphology, Gram staining, and the urease test. Experiments with conventional CD1 and BALB/c mice gave substantially similar results (*24*). Bacterial quantitation was done with streptomycin-resistant derivatives of the *H. pylori* strains used above, which were collected on sterile paper filters, suspended in 0.5 ml of phosphate-buffered saline, serially diluted, and then plated.
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Long-Lasting Neurotrophin-Induced Enhancement of Synaptic Transmission in the Adult Hippocampus

Hyejin Kang and Erin M. Schuman*

The neurotrophins are signaling factors important for the differentiation and survival of distinct neuronal populations during development. To test whether the neurotrophins also function in the mature nervous system, the effects of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophic factor 3 (NT-3) on the strength of synaptic transmission in hippocampal slices were determined. Application of BDNF or NT-3 produced a dramatic and sustained (2 to 3 hours) enhancement of synaptic strength at the Schaffer collateral-CA1 synapses; NGF was without significant effect. The enhancement was blocked by K252a, an inhibitor of receptor tyrosine kinases. BDNF and NT-3 decreased paired-pulse facilitation, which is consistent with a possible presynaptic modification. Long-term potentiation could still be elicited in slices previously potentiated by exposure to the neurotrophic factors, which implies that these two forms of plasticity may use at least partially independent cellular mechanisms.

The neurotrophins are a group of signaling factors that are essential for the regulation of neuronal survival and differentiation during brain development. In the adult rat central nervous system, the hippocampus is a prominent site of expression of BDNF and NT-3 and their receptors (*1*). The expression of BDNF, NT-3, and their receptors can be regulated by neuronal activity (*2–4*), which suggests that the neurotrophins may also participate in synaptic plasticity in the adult central nervous system. Acute exposure to BDNF or NT-3, but not to NGF, rapidly potentiates the frequency of miniature synaptic events at developing neuromuscular synapses in culture (*5*), prompting us to investigate whether the neurotrophins may regulate synaptic strength in the adult brain.

We applied BDNF, NGF, and NT-3 extracellularly and examined their effects on synaptic transmission at the Schaffer collateral-CA1 neuron synapses in hippocampal slices from young adult rats (*6*). Field excitatory postsynaptic potentials (EPSPs) were

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elicited once every 15 s for the duration of the experiment. BDNF and NT-3 (20 ng/ml) (7) both caused a rapid and dramatic enhancement of the initial slope of the field EPSP (Fig. 1, A and B) [mean percent of baseline: BDNF, 279.7 ± 29.2 (n = 13), P < 0.001; NT-3, 235.5 ± 26.0 (n = 11), P < 0.05]. Increases for individual experiments were variable, ranging from 51.3 to 372.6% for BDNF (20 ng/ml) and from 32.0 to 344.7% for NT-3 (20 ng/ml). In contrast, NGF (10 to 20 ng/ml) had no significant effect on synaptic transmission (Fig. 1C) [mean percent of baseline: NGF, 97.6 ± 5.3 (n = 8), not significant (NS)], which is consistent with the apparent lack of TrkA receptor expression in pyramidal neurons of the hippocampus (8). The potentiating effects of NT-3 and BDNF were concentration-dependent: The lowest effective concentration for both neurotrophins was 10 ng/ml; maximal effects were obtained with 20 ng/ml for both BDNF and NT-3 (Fig. 1D). This range of concentrations is similar to that observed for the developmentally significant effects of these factors (9). A single application of BDNF or NT-3 (20 ng/ml) produced the maximal increase in synaptic strength; subsequent applications produced no further increase (10). The enhancement produced by BDNF and NT-3 was not accompanied by any significant or consistent change in presynaptic fiber volley, postsynaptic input resistance, or excitability (11), which suggests a direct alteration of synaptic transmission.

To identify potential downstream effectors of the neurotrophins, we examined whether two different protein kinase inhibitors, K252a and K252b, were capable of blocking the neurotrophin-induced enhancement. Although structurally similar, these two compounds differ in their potency in inhibiting tyrosine kinases (12); K252a (200 nM) is a potent inhibitor of receptor tyrosine kinases, whereas K252b (200 nM) is not. Slices exposed to K252a (200 nM) 30 min before the introduction of BDNF (20 ng/ml) or NT-3 (20 ng/ml) failed to exhibit synaptic enhancement (Fig. 2, A and B) [mean percent of baseline: BDNF, 116.1 ± 7.7 (n = 6), NS; NT-3, 102.4 ± 6.2 (n = 6), NS]. In contrast, BDNF and NT-3 still produced a significant increase in synaptic strength in the presence of K252b (Fig. 2, C and D) [mean percent of baseline: BDNF, 194.3 ± 31.5 (n = 6), P < 0.01; NT-3, 205.2 ± 25.4 (n = 6), P < 0.01], although this increase was slightly less than that observed in the absence of K252b for both BDNF and NT-3. The inhibition of the BDNF- and NT-3–induced enhancement by K252a suggests the involvement of the Trk family of receptor tyrosine kinases.

The longevity of the synaptic enhancement produced by NT-3 and BDNF (Fig. 1, A and B) could reflect either an enduring modification of the synaptic machinery or the inability to wash out the factors from the slice after re-perfusion with normal artificial cerebral spinal fluid (ACSF). To address this issue, we used a protocol in which neurotrophic factor application was followed by an application of K252a, which we showed in the previous experiment (Fig. 2, A and B) could block the effects of both BDNF and NT-3, presumably at the Trk receptor. If the longevity of the observed enhancement were due to residual neurotrophic factor in the tissue, then the subsequent application of K252a should abbreviate the potentiation. To test this, we elicited an enhancement of synaptic transmission by applying BDNF or NT-3 (20 ng/ml) as before. During the washout of the neurotrophic factor, K252a (200 nM) was introduced into the bath. The application of

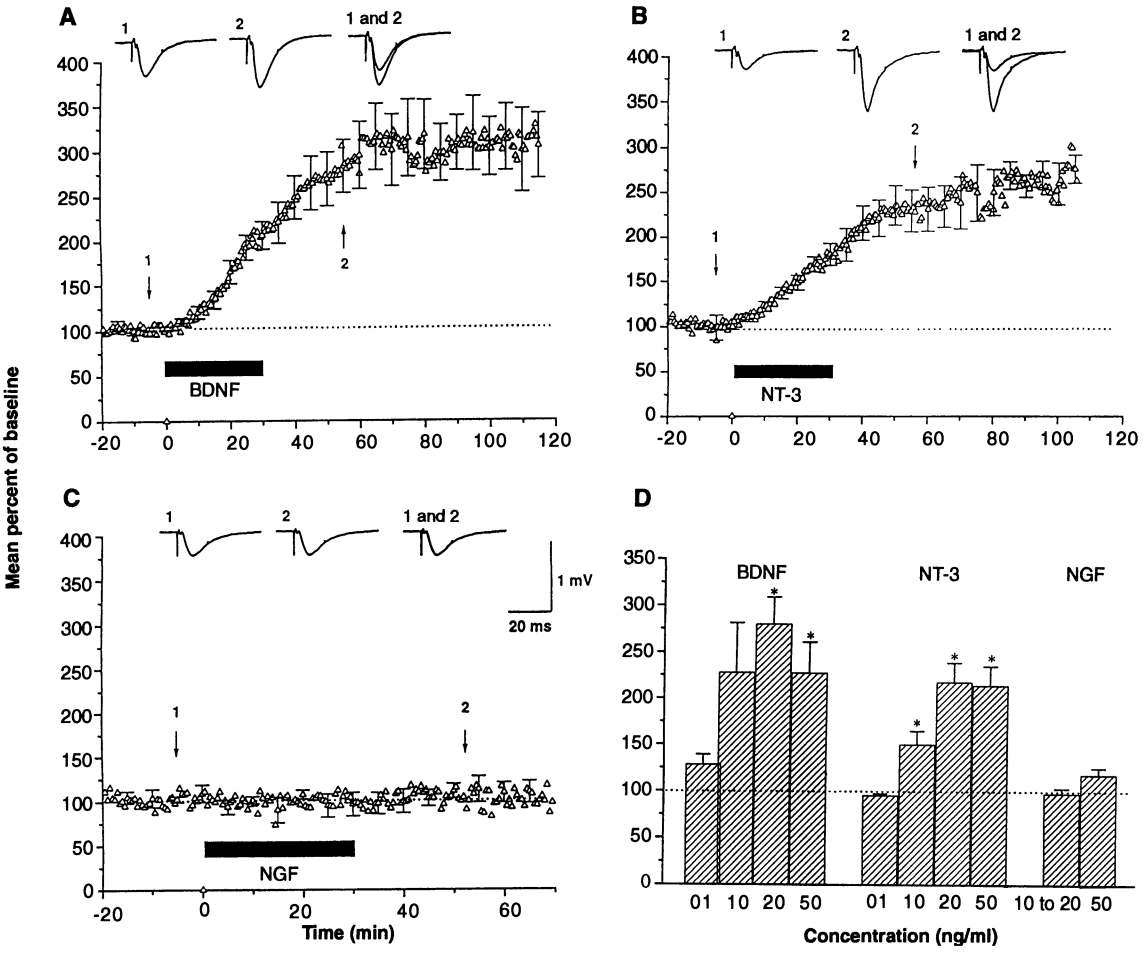

Fig. 1. BDNF and NT-3 enhance excitatory synaptic transmission. (**A**) Ensemble average for all experiments in which BDNF (20 ng/ml) was applied extracellularly. Mean field EPSP slope before BDNF was 0.13 ± 0.01 mV/ms (mean ± SEM) and 0.34 ± 0.03 mV/ms after BDNF. In (A) through (C), two representative field EPSPs are shown for the time points indicated. (**B**) Ensemble average for all experiments in which NT-3 (20 ng/ml) was applied extracellularly. Mean field EPSP slope before NT-3 was 0.11 ± 0.01 mV/ms and 0.34 ± 0.09 mV/ms after NT-3. (**C**) Ensemble average for all experiments in which NGF (10 to 20 ng/ml) was applied extracellularly. (The data for 10 and 20 ng/ml were combined, because they were not significantly different from one another.) Mean field EPSP slope before NGF was 0.14 ± 0.01 mV/ms (mean ± SEM) and 0.13 ± 0.01 mV/ms after NGF. (**D**) Summary graph depicting concentration-response relation for each neurotrophic factor. Asterisks indicate statistical significance at the P < 0.05 level.

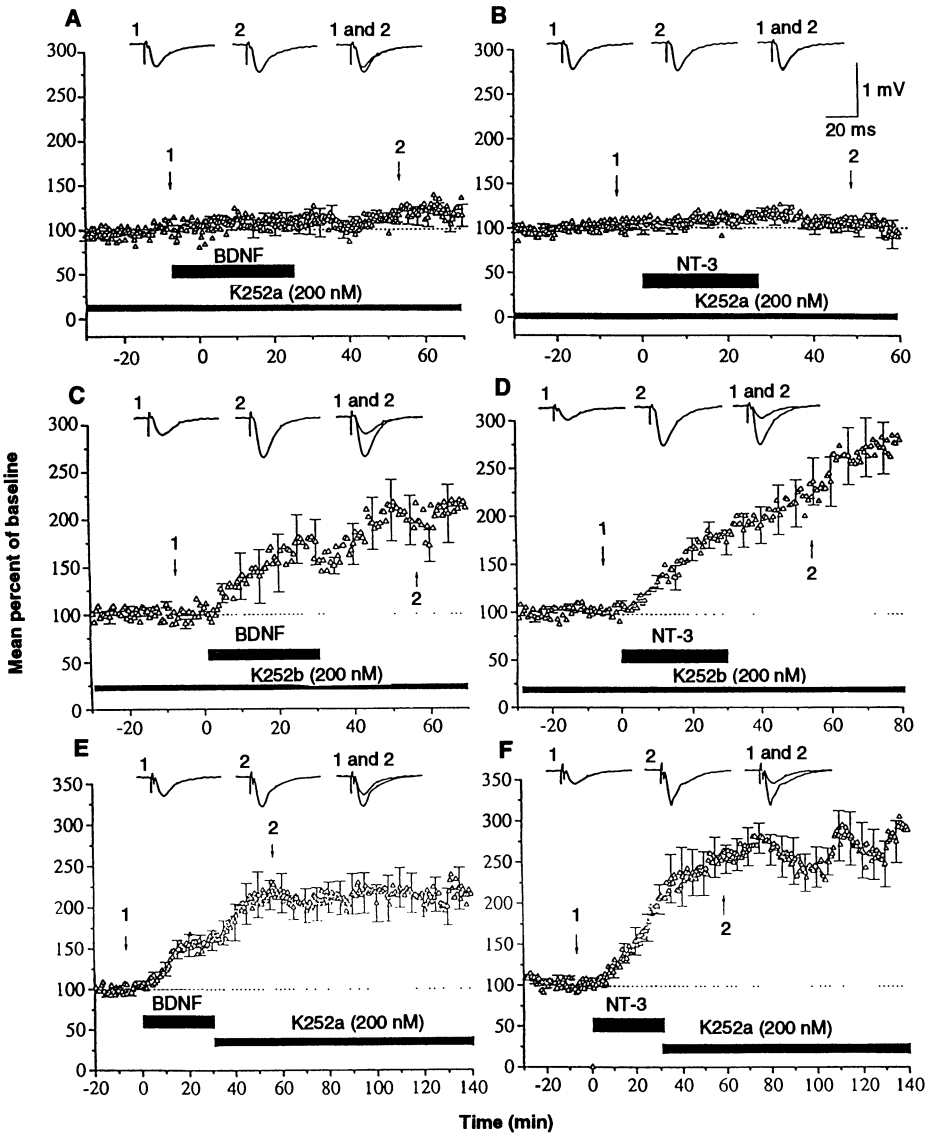

Fig. 2. The effects of BDNF and NT-3 are attenuated by prior treatment with K252a but not by subsequent treatment. (**A**) Ensemble average for all experiments in which BDNF (20 ng/ml) was applied extracellularly in the presence of K252a. Mean field EPSP slope before BDNF was 0.13 ± 0.03 mV/ms (mean ± SEM) and 0.15 ± 0.02 mV/ms after BDNF. In (A) through (F), two representative field EPSPs are shown for the time points indicated. (**B**) Ensemble average for all experiments in which NT-3 (20 ng/ml) was applied extracellularly in the presence of K252a. Mean field EPSP slope before NT-3 was 0.15 ± 0.02 mV/ms and 0.16 ± 0.02 mV/ms after NT-3. (**C**) Ensemble average for all experiments in which BDNF (20 ng/ml) was applied extracellularly in the presence of K252b. Mean field EPSP slope before BDNF was 0.10 ± 0.02 mV/ms and 0.18 ± 0.02 mV/ms after BDNF. (**D**) Ensemble average for all experiments in which NT-3 (20 ng/ml) was applied extracellularly in the presence of K252b. Mean field EPSP slope before NT-3 was 0.14 ± 0.03 mV/ms and 0.26 ± 0.05 mV/ms after NT-3. (**E**) Ensemble average for all experiments in which BDNF (20 ng/ml) was applied extracellularly and then followed by application of K252a. Mean field EPSP slope after 20 to 30 min in the presence of BDNF was 0.18 ± 0.02 mV/ms and 0.24 ± 0.03 mV/ms after 50 to 60 min in the presence of K252a. (**F**) Ensemble average for all experiments in which NT-3 (20 ng/ml) was applied extracellularly and then chased by application of K252a. Mean field EPSP slope after 20 to 30 min in the presence of NT-3 was 0.19 ± 0.01 mV/ms and 0.29 ± 0.03 mV/ms after 50 to 60 min in the presence of K252a.

K252a decreased neither the magnitude nor the duration of the potentiation established by either BDNF or NT-3 (Fig. 2, E and F) [mean percent of baseline: BDNF and $K252a_{pre}$, 155.6 ± 9.1, $K252a_{post}$, 215.3 ± 24.4 (n = 6); NT-3 and $K252a_{pre}$, 173.3 ± 20.4, $K25a_{post}$, 249.9 ± 25.4]. In fact, the enhancement increased further after washout of the factor, as in Fig. 1, which suggests that the long-lasting nature of this enhancement is due to a persistent change initiated by the neurotrophin, rather than to residual factor present in the slice.

During development, neurotrophic factors are thought to be released by postsynaptic target neurons to interact with Trk receptors on axons or growth cones. In the hippocampus, however, BDNF and NT-3 and their receptors TrkB and TrkC are located on both pre- and postsynaptic neurons (*1*), which suggests that these factors could act as autocrine or paracrine signals. To begin to ascertain the mechanism by which BDNF and NT-3 enhance synaptic strength, we examined whether these factors affect paired-pulse facilitation (PPF). PPF is a form of short-term plasticity in which the size of the postsynaptic response to the second of two closely spaced (less than 500 ms) stimuli is increased, presumably because of enhanced neurotransmitter release from residual Ca^{2+} in the presynaptic nerve terminal (*13*). Manipulations that enhance neurotransmitter release usually decrease the magnitude of PPF (*14*). We thus compared the magnitude of PPF before and after treatment with BDNF and NT-3. Both BDNF and NT-3 significantly decreased PPF (Fig. 3, A and B), which suggests a presynaptic mode of action. The reduction in PPF was not due to neurotrophin-induced saturation of postsynaptic responses because decreasing the stimulus strength to match the size of the postsynaptic response before BDNF and NT-3 treatment did not abolish the attenuation of PPF by the factors (*15*).

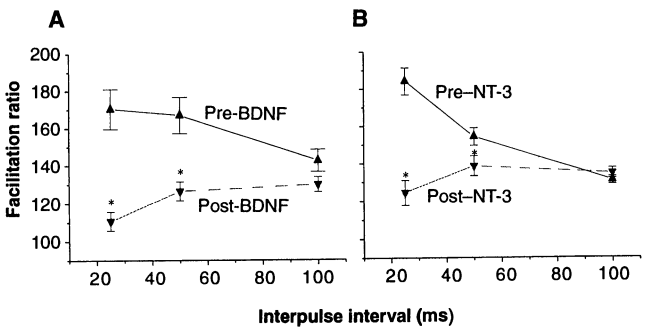

Fig. 3. BDNF and NT-3 decrease PPF. Both plots show the facilitation ratios [slope of second EPSP/slope of first EPSP] for three different interstimulus intervals: 100, 50, and 25 ms before (solid triangle) and after (inverted triangle) the addition of the factor. BDNF (**A**) and NT-3 (**B**) significantly decreased PPF at the 50- and 25-ms interpulse intervals.

The rapid onset and longevity of the neurotrophin-induced enhancement are similar to those observed during long-term potentiation (LTP) induced by high-frequency stimulation. Accordingly, we tested

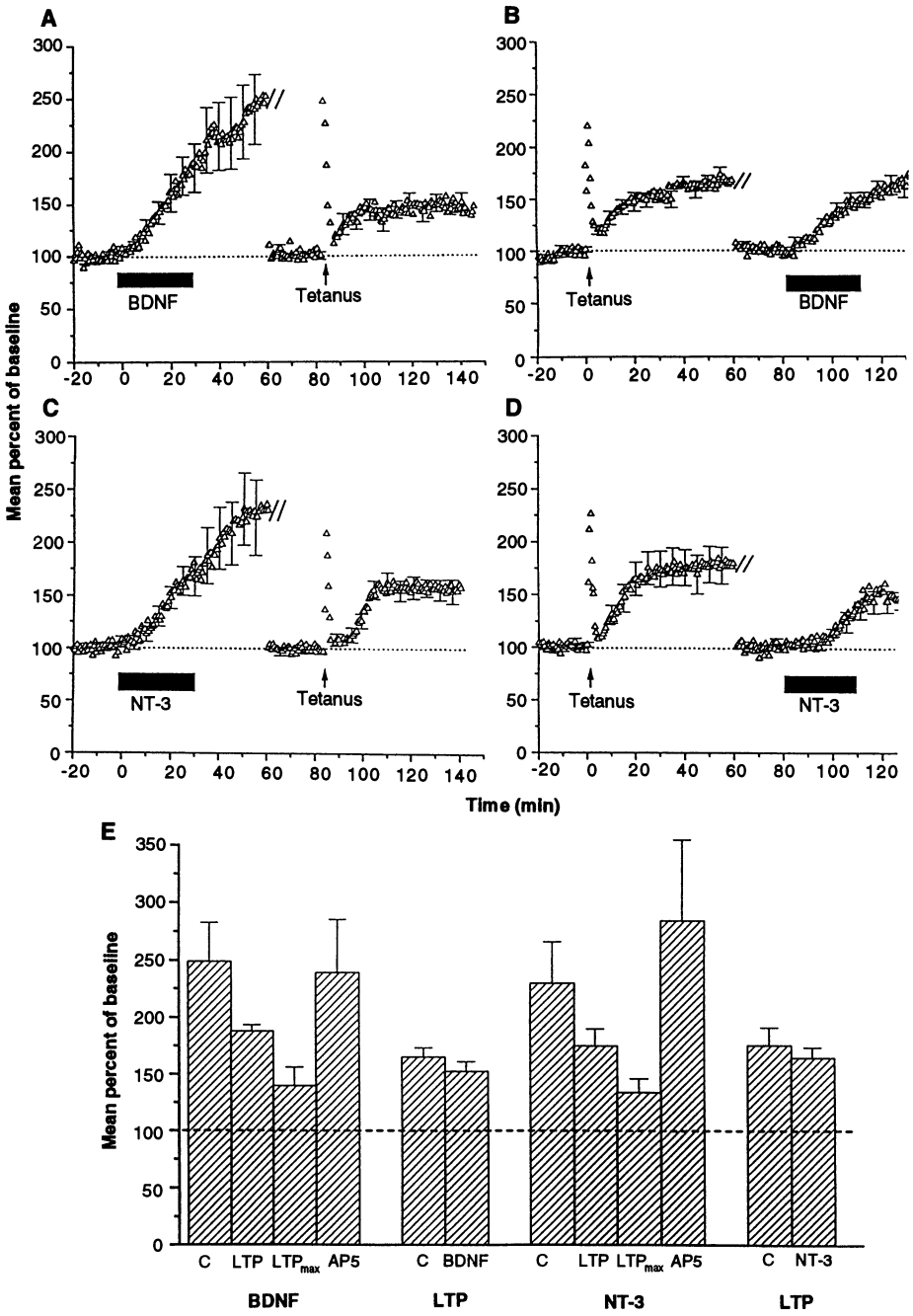

Fig. 4. Neurotrophin-induced potentiation and LTP do not significantly occlude one another. In (A) though (D) the stimulus intensity was reduced to match the size of the field EPSP to control levels at the time indicated by the two slanted bars. (**A**) Ensemble average showing experiments in which BDNF-induced potentiation was followed by tetanic stimulation to induce LTP. LTP could still be elicited at synapses previously potentiated by BDNF. (**B**) Ensemble average showing experiments in which LTP was followed by BDNF (20 ng/ml) application. BDNF was still capable of enhancing transmission at potentiated synapses, although the magnitude of the enhancement was slightly less than that observed in control pathways. (**C**) Ensemble average showing experiments in which NT-3–induced potentiation was followed by tetanic stimulation to induce LTP. LTP could still be elicited at synapses previously potentiated by NT-3. (**D**) Ensemble average showing experiments in which LTP was followed by NT-3 (20 ng/ml) application. NT-3 was still capable of enhancing transmission at potentiated synapses, although the magnitude of the enhancement was slightly less than that observed in control pathways. (**E**) Summary plot showing the magnitude of potentiation produced at LTP-induced or neurotrophin-treated synapses in naive (control, C) slices or slices previously exposed to a neurotrophic factor, normal LTP induction (LTP), maximal LTP induction (LTP_{max}), or an NMDA receptor antagonist (AP5).

whether the neurotrophin-induced potentiation might share common cellular mechanisms with synaptically induced LTP by testing the ability of each form of potentiation to occlude subsequent induction of the other form. We first applied either tetanic stimulation or a neurotrophic factor and allowed the potentiation to develop and stabilize for 1 hour. At this time, the stimulus intensity was adjusted to match the size of the field potential to the prepotentiation level. Potentiation was then induced by the second mechanism. We found that prior enhancement of synaptic transmission by BDNF or NT-3 did not occlude synaptically induced LTP (Fig. 4, A, C, and E) [mean percent of baseline: $LTP_{control}$ = 165.3 ± 7.8 (n = 8); $LTP_{post\text{-}BDNF}$ = 152.4 ± 8.6 (n = 8), NS; $LTP_{control}$ = 175.8 ± 15.3 (n = 8); $LTP_{post\text{-}NT\text{-}3}$ = 164.5 ± 9.1 (n = 8), NS]. Prior induction of LTP slightly, although not significantly, attenuated the subsequent potentiation by BDNF or NT-3 (Fig. 4, B, D, and E) [mean percent of baseline: $BDNF_{control}$ = 248.9 ± 33.5 (n = 8); $BDNF_{post\text{-}LTP}$ = 184.8 ± 5.5 (n = 8) NS; $NT\text{-}3_{control}$ = 230.1 ± 35.9 (n = 8); $NT\text{-}3_{post\text{-}LTP}$ = 175.2 ± 14.8 (n = 8), NS]. Delivery of repeated trains of tetanic stimulation to maximally induce LTP (*16*) further reduced the amount of potentiation elicited by BDNF or NT-3, although each factor still significantly enhanced synaptic transmission [mean percent of baseline: $BDNF_{post\text{-}LTP}$ = 139.7 ± 16.3 (n = 5), $P < 0.05$; $NT\text{-}3_{post\text{-}LTP}$ = 133.8 ± 12.2 (n = 5), $P < 0.05$]. As shown in Fig. 4, on average the LTP developed with a fairly slow time course (~10 min). In a separate set of experiments, we confirmed that the LTP induced by the above stimulation parameters relies on the activation of *N*-methyl-D-aspartate (NMDA) receptors by conducting experiments in the presence of the NMDA receptor antagonist AP5 [mean percent of baseline: AP5 (50 μM) = 98.1 ± 3.7 (n = 4) (*10*)]. In contrast, we found that both BDNF and NT-3 (20 ng/ml) could still enhance synaptic transmission in the presence of AP5 (50 μM) (Fig. 4E) [mean percent of baseline: BDNF, 239.2 ± 45.6 (n = 6), $P <$ 0.05; NT-3, 284.1 ± 70.3 (n = 6), $P <$ 0.05]. Taken together, these data suggest that these two forms of synaptic enhancement may involve at least partially independent cellular mechanisms. Although synaptic potentiation elicited by BDNF or NT-3 did not prevent subsequent LTP measured 1 hour after induction, it is still possible that the neurotrophin-induced enhancement may interact with later phases of LTP that appear to rely on protein synthesis (*17*, *18*).

These experiments demonstrate that BDNF and NT-3 produce rapid changes in synaptic transmission at mature synapses. Both BDNF and NT-3 decrease PPF but do not interact significantly with the early (less than 1 hour) phase of LTP, which is consistent with previous observations that have failed to detect any interaction of PPF

with LTP in CA1 (*14*). Therefore, there are likely to be at least two independent mechanisms by which synaptic strength can be enhanced at these synapses. The mRNA levels for BDNF and NT-3 are enhanced after tetanic stimulation (*3*), however, which suggests that the synaptic enhancement documented here may contribute to later phases of LTP. Taken together, these data and a previous study (*5*) suggest that one action of neurotrophins may be to alter synaptic strength acutely in the period of time preceding the long-term structural changes that underlie developmental and adult plasticity.

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6. Hippocampal slices were prepared from young adult male Sprague-Dawley rats (mean age = 46.8 ± 1.4 days). Slices were submerged in a stream of ACSF (flow rate 250 ml/hour) (119 mM NaCl, 2.5 mM KCl, 1.3 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.0 mM NaH_2PO_4, 26.2 mM $NaHCO_3$, and 11.0 mM glucose) maintained at room temperature (22° to 25°C) and gassed with 95% O_2 and 5% CO_2. Field EPSPs, measured in the stratum radiatum, were evoked by stimulation of the Schaffer collateral-commissural afferents (once every 15 s); the initial (1 to 2 ms) slope was measured. Percent baseline values are reported for 1 hour after neurotrophin addition or LTP induction. Input resistance was monitored before and after neurotrophin application by current injection through intracellular recording electrodes placed in the stratum pyramidale of CA1. Ensemble average plots represent group means of each EPSP, for all experiments, aligned with respect to the time of neurotrophin application or LTP induction (four individual 100-Hz trains delivered for 1 s each at the test intensity; intertrain interval = 15 s). To assess statistical significance, paired *t* tests were done on nonnormalized data, comparing mean EPSP slope values for the 10 min preceding the application of the neurotrophin to values 50 to 60 min after application. *P* values greater than 0.05 are designated as NS.
7. Great care was taken in the application and storage of the neurotrophic factors. BDNF and NT-3 were kept at −70°C; phosphate buffer stock solutions were made every 1 to 3 days and kept at 4°C. NGF (R&D Systems, Minneapolis, MN) was kept at 4°C. New supplies of NT-3 and BDNF were obtained on a regular basis (every 2 to 4 months), as it was observed that individual stocks became less potent over time. BDNF was prepared in phosphate-buffered saline (PBS) and NT-3 was prepared in 0.5% sucrose and 4.5% mannitol. Application of vehicle alone at the appropriate dilutions (10^{-5} to 10^{-6}) had no effect on synaptic transmission. The perfusion apparatus was modified to include chemically inert materials: silicon tubing and a Teflon beaker. Bovine serum albumin was not used as a carrier, because previous work (*19*) has suggested that it has independent effects on synaptic transmission and LTP in the hippocampus. The K252 compounds (Kamiya Biochemical, Thousand Oaks, CA) were kept as 10^4 stock solutions in dimethyl sulfoxide (DMSO) at 4°C. The final concentration of DMSO in our experiments was 0.01%, which has no detectable effect on synaptic transmission.
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11. The amplitude of the presynaptic fiber volley did not change significantly after treatment with BDNF (20 ng/ml) (mean percent of baseline: 106.2 ± 3.6; n = 12) or NT-3 (20 ng/ml) (mean percent of baseline: 107.0 ± 4.1; n = 11). The input resistance of CA1 neurons did not change significantly after treatment with BDNF (50 ng/ml) (mean percent of baseline: 94.0 ± 7.2; n = 6) or NT-3 (50 ng/ml) (mean percent of baseline: 87.6 ± 11.9; n = 5). Although simultaneous measurements of the population spike in the CA1 pyramidal cell layer revealed significant increase in amplitude on exposure to either BDNF or NT-3 [mean percent of baseline: BDNF, 2530.0 ± 60.5% (n = 3); NT-3, 230.7 ± 47.0% (n = 3)], multiple population spikes were never observed as would be expected if the slice were exhibiting epileptic activity or large increases in neuronal excitability.
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15. PPF was examined at three interstimulus intervals: 100, 50, and 25 ms. BDNF decreased PPF to 92.0, 77.4, and 66.9% of control levels (n = 7), respectively, without reducing the stimulus strength, and to 93.7, 78.0, and 67.8% of control levels (n = 3) when the stimulus strength was reduced to match the size of the field EPSP to pre-BDNF levels. PPF after NT-3 application was 103.0, 90.0, and 67.7% of control levels (n = 6) without stimulus readjustment, and 108.6, 89.4, and 74.9% of control levels (n = 2) with stimulus readjustment. PPF measurements were made from 30 to 90 min after neurotrophin washout. PPF after LTP was 108.1, 104.4, and 100.3% of control levels (n = 4) without stimulus readjustment.
16. To maximally induce LTP, we delivered two to four sets of tetanic stimulation (one set = four trains of 100-Hz stimulation delivered for 1 s; inter-train interval = 15 s, inter-set interval = 5 to 20 min) until the field EPSP had reached its apparent maximum value and no further potentiation could be elicited. This stimulation protocol resulted in LTP of the following magnitude: mean percent of baseline ± SEM: 183.6 ± 23.4% (n = 10). The magnitude of this potentiation was not significantly different from the potentiation obtained with the use of normal induction protocols (one set of tetanic stimulation) [170.5 ± 8.4% (n = 16)].
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Inhibition of Ocular Dominance Column Formation by Infusion of NT-4/5 or BDNF

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During the development of the visual system of higher mammals, axons from the lateral geniculate nucleus (LGN) become segregated into eye-specific patches (the ocular dominance columns) within their target, layer 4 of the primary visual cortex. This occurs as a consequence of activity-dependent synaptic competition between axons representing the two eyes. The possibility that this competition could be mediated through neurotrophin-receptor interactions was tested. Infusion of neurotrophin-4/5 (NT-4/5) or brain-derived neurotrophic factor (BDNF) into cat primary visual cortex inhibited column formation within the immediate vicinity of the infusion site but not elsewhere in the visual cortex. Infusion of nerve growth factor, neurotrophin 3 (NT-3), or vehicle solution did not affect column formation. These observations implicate TrkB, the common receptor for BDNF and NT-4/5, in the segregation of LGN axons into ocular dominance columns in layer 4. Moreover, they suggest that in addition to their better known roles in the prevention of cell death, neurotrophins may also mediate the activity-dependent control of axonal branching during development of the central nervous system.

One of the principal mechanisms thought to drive the refinement of specific sets of neural connections during development is activity-dependent competition between presynaptic axons for postsynaptic target neurons (*1*). Perhaps the best studied example of this competition in the central nervous system is the formation of ocular dominance columns in the visual cortex of highly binocular mammals such as carnivores and primates. The anatomical basis for the ocular dominance columns is the segregation of axonal inputs from the LGN into alternating, eye-specific patches within layer 4 (*2*). Early in development, however, LGN axons from the two eyes are intermixed with each other in layer 4. The eye-specific patches emerge gradually over a postnatal period of 4 to 6 weeks in the cat as LGN axons remodel and restrict their terminal arbors (*3*, *4*). Experimental perturbations of neural activity have given rise to the idea that competitive interactions be-

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